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Nonsteroidal progesterone receptor ligands (I): Synthesis and SAR of new tetrahydronaphthofuranone derivatives

Rie Shinei,* Ken-ichi Kurihara, Kiyoshi Tanabe, Yuji Tabata, Yasushi Kurata, Shigeru Hoshiko and Tsuneo Okonogi

Pharmaceutical Research Department, Meiji Seika Kaisha, Ltd., 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan

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Abstract—We have synthesized a series of nonsteroidal progesterone receptor (PR) ligands, tetrahydronaphthofuranones, structurally based on the fungal metabolite PF1092C. Structure–activity relationship studies revealed that substituents at the 6- and 7-positions were critical for PR binding affinity and for agonist or antagonist activity. Compounds in this series, exemplified by **19i**, exhibited high affinity and high specificity for PR over other steroid hormone receptors and acted as selective PR antagonists. Further modification of PF1092C may generate compounds of potential pharmacological interest.

1. Introduction

Progesterone receptor (PR) antagonists have been the subject of research since the 1980s. RU486 (mifepristone), the only clinically available PR antagonist, has been identified as having potential therapeutic effects for patients with breast cancer,[1] endometriosis,[2] uterine leiomyoma,[3] and meningioma[4] in clinical trials. Numerous related compounds have been synthesized since the structure of RU486 was made public.[5,6] However, RU486 and related compounds possess a steroidal skeleton, which results in the appearance of side effects associated with cross-reactivity with other steroid receptors, especially glucocorticoid receptors.[7,8] As a result, interest has recently been focused on nonsteroidal PR antagonists.[9–14]

In the course of our microbial screening studies to find novel nonsteroidal PR ligands, the fungal metabolites PF1092A (**1**), B (**2**), and C (**3**) (Fig. 1) were isolated from extracts of cell cultures of the rare fungus *Penicillium oblatum* PF1092.[15,16] Structurally, they belong to the class of complex eremophilane-type sesquiterpenes, with four contiguous *syn*-substituents at the 4a-, 5-, 6-, and 7-positions in the 4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one skeleton. PF1092A (**1**) and PF1092B (**2**) showed high and low affinity, respectively, for PR in vitro. We therefore carried out structural modifications of the skeleton with totally synthetic methods to investigate the structure–activity relationship (SAR) of racemic **1** and its analogues.[17–20] We found that the substituent at the 6- or 7-position of tetrahydronaphthofuranone is critical for binding affinity to PR in vitro. These results suggested that derivatives of **3** might be good candidates for potent and specific nonsteroidal PR ligands and prompted us to further explore the SAR of 4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one.

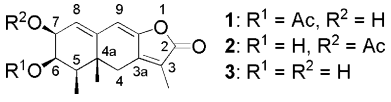

Figure 1. Structure of PF1092A (**1**), B (**2**), and C (**3**).

Herein we report the syntheses of a novel series of PR ligands, in which the hydroxyl group(s) at the 6- and/or 7-positions of **3** are modified. The human PR binding affinities and functional activities of several members of this series are also presented.

Keywords: Nonsteroidal progesterone receptor ligands; PR antagonist; Tetrahydronaphthofuranone; PF1092.
* Corresponding author. Tel.: +81 45 541 2521; fax: +81 45 543 9771; e-mail: rie_shinei@meiji.co.jp

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2. Chemistry

2.1. Compounds with 6,7-*syn* substituents

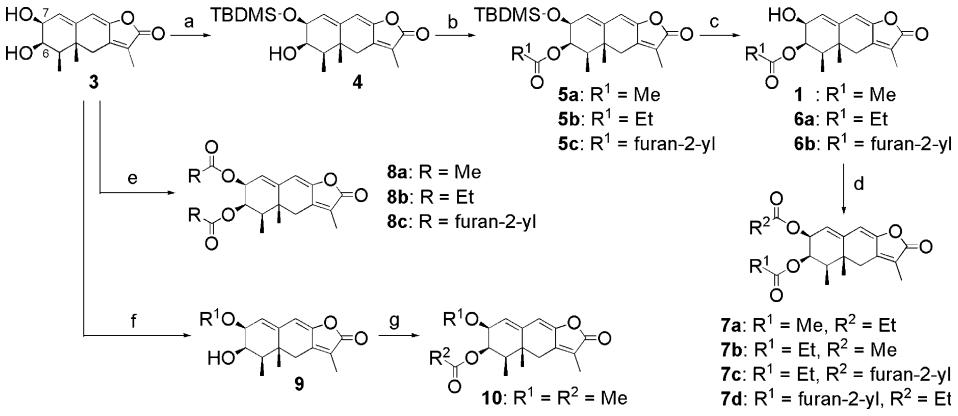
Various derivatives with 6,7-*syn* substituents were synthesized as shown in Scheme 1. PF1092C (**3**) has free secondary hydroxyl groups at the 6- and 7-positions, and the 7β-carbinol is the more reactive of the two because of its allylic position. Therefore, acylation of **4**, which was prepared by protection of the 7β-allyl alcohol of **3** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in DMF, afforded **5**. Removal of the silyl moiety of **5** with hydrogen fluoride–pyridine complex (Py–HF) in THF provided the monoacyl compounds **6a**, **6b**, and **1**. Furthermore, the hetero-diesters **7a–d** were obtained by a second acylation of the 7β-hydroxyl group with a different acid chloride and 4-dimethylaminopyridine (DMAP). On the other hand, diacylation of **3** with an excess of acid anhydride or acid chloride afforded the homo-diesters **8a–c**. Alkylation of **3** with alkyl halide and sodium hydride (NaH) and subsequent acylation of the 6-hydroxyl group led to the 7β-alkyloxy compound **10**.

2.2. Compounds with 6,7-*anti* substituents

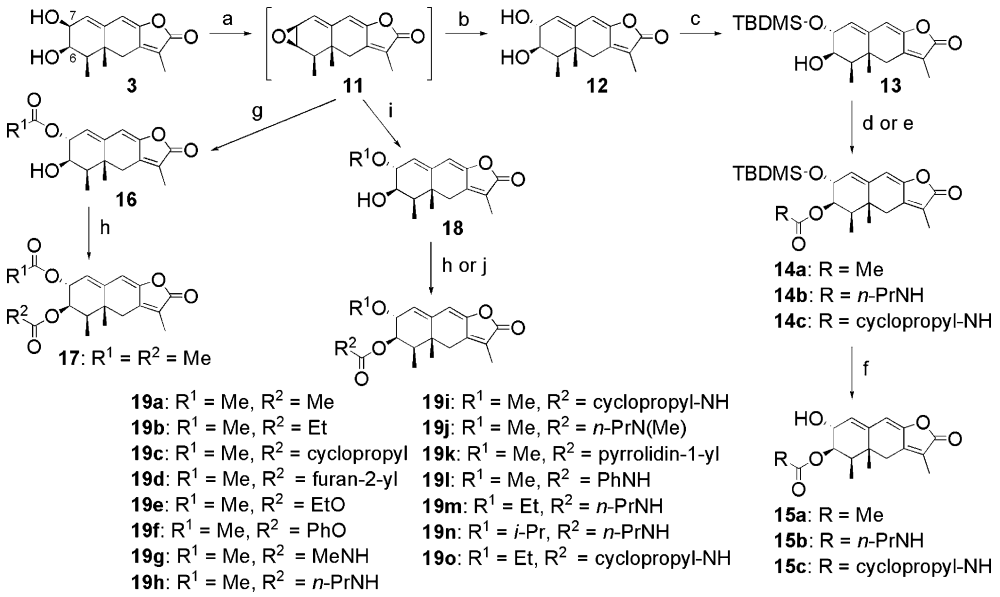
The 6,7-*anti* derivatives were prepared from **3** as shown in Scheme 2. Conversion of the 7-position to α-configuration was achieved through the β-epoxide **11**, which was generated by mesylation of **3** with methanesulfonyl chloride (MsCl) and *N*,*N*-diisopropylethylamine followed by alkaline work-up with 1 N NaOH. The ^{1}H NMR spectrum of **11** revealed *syn*-configuration at C-5, C-6, and C-7, based on the coupling constants (δ_H 3.43; 1H, dd, $J_{6,7}$ = 4.2 Hz, $J_{5,6}$ = 1.0 Hz, H-6) and NOE between H-5 and H-6. Furthermore, the ^{13}C NMR spectrum of **11** showed that the signals of C-6 of **3** at δ_C 72.4 and C-7 of **3** at 69.0 were shifted upfield to δ_C 62.0 and 48.3, respectively. The intermediates with a 7α-substituent, **12**, **16**, and **18**, were synthesized by nucleophilic displacement reaction of **11** with water, carboxylic acid or alcohol. Thus, the 7α-hydroxy-6β-ester **15a** was derived from **12** by the sequence, silyl protection of the 7α-hydroxyl group, acetylation of the 6β-hydroxyl group, and deprotection of the silyl moiety at the 7-position with tetrabutylammonium fluoride (TBAF). After protection of the 7α-hydroxyl group of **12**, the carbamates **15b** and **15c** were obtained by reaction of 1,1′-carbonyldiimidazole (CDI) at the 6-position. The intermediate, the 1*H*-imidazol-1-carboxylate, afforded carbamates with an excess of amine in toluene. Additionally, the *anti*-diacyl compound **17** was obtained from **11** through a two-step procedure involving 7α-carboxylation and acylation at the 6-position. The alcohols **18**, which were prepared by nucleophilic displacement reaction of **11** with various alcohols, were led to 7α-alkyloxy derivatives, such as esters **19a–d** and carbonates **19e**,**f** by routine methods. In the syntheses of carbamates **19g–i**, methyl trifluoromethanesulfonate (TfOMe) was effective to decrease the amount of amines and reaction time. In the case of usage with less reactive secondary amines and aromatic amines (anilines), TfOMe was required to obtain carbamates **19j–l**. To prepare **19m–o**, having the large substituents at the 7-position, TfOMe was also required.

2.3. 7-Deoxy compounds

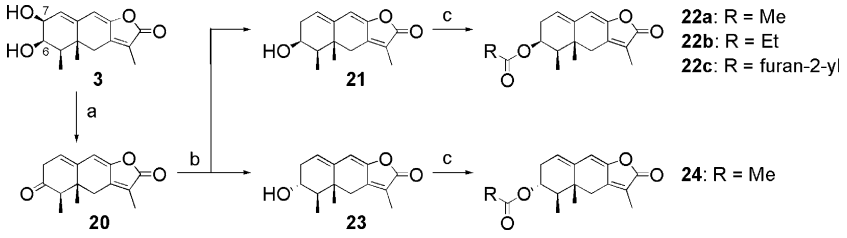
In addition, the *syn*-diol **3** was converted to the ketone **20** by dehydration with *p*-toluenesulfonic acid (*p*-TsOH) in toluene at 60 °C for 10 min as depicted in Scheme 3. Reduction of **20** using sodium borohydride ($NaBH_4$) in methanol at room temperature for 30 min afforded the major 6-hydroxy product **21** in 56% together with a small amount of the minor 6-hydroxy compound **23** (**21**:**23** = 39:1). The ^{1}H NMR spectrum of **21** indicated *syn*-configuration at C-5 and C-6, based on the coupling constants between H-5 and H-6 ($J_{5,6}$ = 2.5 Hz). Moreover, the ^{1}H NMR spectrum of **21** identified with that of the previously reported racemic 6β-hydroxy compound.[17] On the other hand, compound **23** was proved to be *anti*-configuration at C-5 and C-6 owing to the coupling constants, which revealed axial–axial configuration between H-5 and H-6 ($J_{5,6}$ = 10.5 Hz). Additionally, NOE was obviously observed between H-6 and Me-4a in **23**. According to these distinctions between **21** and **23**, the stereochemistry of 6-hydroxyl group of **21** was determined as 6β and that of **23** was as 6α.



Scheme 1. Synthesis of 6,7-*syn* derivatives. Reagents: (a) TBDMSCl, imidazole, DMF; (b) R^1COCl, DMAP, CH_2Cl_2; (c) Py–HF complex, THF; (d) R^2COCl, DMAP, CH_2Cl_2; (e) $(RCO)_2O$ or RCOCl, *i*-Pr_2NEt, CH_2Cl_2; (f) R^1X, NaH, DMF; (g) R^2COCl, pyridine, CH_2Cl_2.



Scheme 2. Synthesis of 6,7-*anti* derivatives. Reagents: (a) 1—MsCl, *i*-Pr_2NEt, CH_2Cl_2, 2—1 N NaOH; (b) 0.5 N HCl, MeCN; (c) TBDMSCl, imidazole, DMF; (d) AcCl, pyridine, CH_2Cl_2; (e) 1—CDI, CH_2Cl_2, 2—amine, toluene; (f) TBAF, THF; (g) R^1COOK, 18-crown-6, MeCN; (h) R^2COCl, pyridine, CH_2Cl_2; (i) R^1OH, H^+, CH_2Cl_2; (j) 1—CDI, CH_2Cl_2, 2—amine, TfOMe, THF.



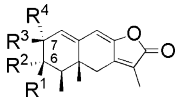
Scheme 3. Synthesis of 7-deoxy derivatives. Reagents: (a) *p*-TsOH, toluene; (b) $NaBH_4$, MeOH; (c) RCOCl, pyridine, CH_2Cl_2.

The stereoselectivity of this reduction thought to be caused by that α face attack of hydride to the ketone at the 6-position in **20** was superior because of the steric hindrance of 5β-methyl group. Conventional acylation of **21** and **23** led to the 6β-esters **22a**–**c** and 6α-ester **24**, respectively.

3. Results and discussion

The synthesized compounds were evaluated for their ability to inhibit the binding of [^{3}H]progesterone to human PR in human breast carcinoma (T47D) cells. The relative binding affinity (RBA) values are summarized in Tables 1–5. The RBA was calculated according to the following equation: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100. Functional activity of the compounds was further assessed by using the progesterone-dependent exogenous luciferase (LUC) expression assay in T47D cells. In this assay, T47D cells were transfected with the exogenous reporter gene, using plasmid pMANneo-LUC. The compounds were evaluated in the presence or absence of progesterone (i.e., in antagonistic and agonistic formats, respectively). We classified the modulation of LUC expression into four types according to the following criteria:

Table 1. Human PR binding affinities of acetates

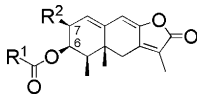


Compound	R^1	R^2	R^3	R^4	RBA[†]	LUC assay[¶]
22a	AcO	H	H	H	15	c
24	H	AcO	H	H	1	n.t.[§]
2	HO	H	AcO	H	1	c
16	HO	H	H	AcO	<0.3	n.t.[§]
1	AcO	H	HO	H	11	c
Progesterone[‡]					100	d

[†] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.
[‡] IC_{50} value of progesterone: 32 nM.
[§] Not tested.
[¶] The classification of the potency in LUC assay was defined as described in the text.

Type a. Suppression of LUC expression (antagonistic activity) ⩾90% in the antagonist format and stimulation of LUC expression (agonistic activity) < 10% in the agonist format.
Type b. Antagonistic activity 90–75%, agonistic activity 10–25%.
Type c. Antagonistic activity 74–25%, agonistic activity 26–74%.

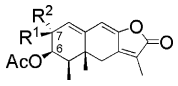
Table 2. Human PR binding affinities of 6,7-*syn* esters



Compound	R^1	R^2	RBA[†]	LUC assay[§]
22a	Me	H	15	c
1	Me	HO	11	c
8a	Me	AcO	13	a
7a	Me	EtCOO	6	b
22b	Et	H	30	c
6a	Et	HO	9	c
7b	Et	AcO	6	b
8b	Et	EtCOO	20	a
7c	Et	Furan-2-ylcarbonyloxy	2	c
22c	Furan-2-yl	H	49	c
6b	Furan-2-yl	HO	63	c
7d	Furan-2-yl	EtCOO	16	c
8c	Furan-2-yl	Furan-2-ylcarbonyloxy	3	c
Progesterone[‡]			100	d

[†] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.
[‡] IC_{50} value of progesterone: 32 nM.
[§] The classification of the potency in LUC assay was defined as described in the text.

Table 3. Human PR binding affinities of 6-acetates



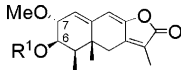
Compound	R^1	R^2	RBA[†]	LUC assay[§]
22a	H	H	15	c
15a	H	HO	4	b
19a	H	MeO	5	c
17	H	AcO	2	c
1	HO	H	11	c
10	MeO	H	1	a
8a	AcO	H	13	a
Progesterone[‡]			100	d

[†] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.
[‡] IC_{50} value of progesterone: 32 nM.
[§] The classification of the potency in LUC assay was defined as described in the text.

Type d. Antagonistic activity <25%, agonistic activity ⩾75%.

The human PR affinities of a series of acetates (**16**, **22a**, and **24**) and natural products (**1** and **2**) were determined (Table 1). Previous work has suggested that binding affinity for human PR is affected by modification at the 7-position of tetrahydronaphthofuranones.[20] The data for the compounds in Table 1 throw light on the roles of the acetyl groups at the 6- and 7-positions. The 6β-acetoxy groups of **1** and **22a** provided the highest binding affinity. The absence of a 6β-acetoxy group, as in the series 7β- (**2**), 7α- (**16**), and 6α- (**24**), resulted in a marked drop in binding potency. The difference in RBA between the 6β-acetate **22a** and its epimer **24** was as large as 15-fold. A 7-hydroxyl group may replace

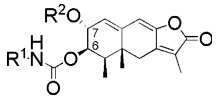
Table 4. Human PR binding affinities of 6,7-*anti* derivatives



Compound	R^1	RBA[†]	LUC assay[§]
19b	EtCO	10	c
19c	Cyclopropylcarbonyl	11	c
19d	Furan-2-ylcarbonyl	39	d
19e	EtOCO	6	b
19f	PhOCO	5	a
19g	MeNHCO	62	c
19h	*n*-PrNHCO	9	a
19i	Cyclopropyl-NHCO	24	a
19j	*n*-PrN(Me)CO	56	c
19k	Pyrrolidin-1-ylcarbonyl	20	c
19l	PhNHCO	2	a
Progesterone[‡]		100	d

[†] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.
[‡] IC_{50} value of progesterone: 32 nM.
[§] The classification of the potency in LUC assay was defined as described in the text.

Table 5. Human PR binding affinities of 6,7-*anti* carbamates



Compound	R^1	R^2	RBA[†]	LUC assay[§]
15b	*n*-Pr	H	19	b
19h	*n*-Pr	Me	9	a
19m	*n*-Pr	Et	16	a
19n	*n*-Pr	*i*-Pr	2	a
15c	Cyclopropyl	H	10	a
19i	Cyclopropyl	Me	24	a
19o	Cyclopropyl	Et	9	a
Progesterone[‡]			100	d

[†] Relative binding affinity (RBA) was calculated as follows: RBA = (IC_{50} of progesterone/IC_{50} of test compound) × 100.
[‡] IC_{50} value of progesterone: 32 nM.
[§] The classification of the potency in LUC assay was defined as described in the text.

a hydrogen atom (compare **1** and **22a**). In order to seek even more potent compounds, we decided to explore the SAR of the 6β-ester derivatives. The results are summarized in Table 2.

We next replaced the 7β-substituent and the 6β-ester moiety. The modification resulted in changes of both the radioligand binding and LUC activities. Compounds with a hydrogen atom at the 7-position (**22a–c**) showed the highest binding affinity, but exhibited an agonistic character. Increasing the bulkiness of substituents at the 6- and especially 7-positions reduced the binding potency. Aliphatic diesters (cf. **7a**, **7b**, **8a**, and **8b**) showed higher antagonistic activity than the aromatic esters, which were categorized as Type c. Esters that contained a furan ring included compounds (**6b**, **22c**) with the highest binding affinity (RBA = 63 and 49). Interestingly, the diacetate **8a** and dipropionate **8b** were

as potent as **1** and **22a**, and showed the desired antagonistic nature (Type a).

We extended our investigation to 6,7-*anti* tetrahydronaphthofuranones having a 6β-acetoxy group, as summarized in Table 3. Replacement of the 7β-substituent, such as hydroxyl (**1**) or acetoxy (**8a**), with the corresponding 7α-substituent (**15a** and **17**, respectively) significantly reduced the binding affinity. Exceptionally, the 7β-methoxy acetate **10** showed a dramatically low affinity, and the 7α-methoxy analogue **19a** displayed a slightly higher binding potency. Several of the 7β-hydroxy and 7-deoxy derivatives were unstable, so an alternative series of more stable compounds, **3**, was devised to expedite SAR exploration of the 7α-methoxy series (Table 4).

Next, we modified the substituents at the 6-position in an attempt to obtain human PR antagonists with higher binding affinity. Conversion of the 6β-esters to carbonates (**19e** and **19f**) resulted in a several-fold decrease in binding potency (Table 4). Structural changes at the 6-position led to relative changes in binding and LUC activities, and a declining trend of affinity was observed across the antagonistic compounds (Type a). Aliphatic carbamates showed retention or enhancement of both binding and antagonistic potency, as seen with the *n*-propyl and cyclopropyl carbamate analogues **19h** and **19i**. Although compounds such as **19g** and **19j** displayed the highest binding affinity, they had lost antagonistic activity (Type c). The aromatic carbamate **19l** showed a significant reduction of binding ability.

We thoroughly investigated the SAR of the 7α-substituent of 6β-carbamates and the results are shown in Table 5. Most of the compounds were found to be antagonists, with a good correlation between the observed binding affinity and functional activity. The methoxy analogue **19i** was the most potent human PR antagonist. Replacement of the methoxy group of **19h** with the largest *iso*-propyl group (**19n**) only led to a decrease in potency.

The representative dose-dependency of functional activity in the LUC assay is shown in Figure 2. The compounds were evaluated in the presence or absence of progesterone (i.e., in antagonistic and agonistic formats, respectively) and classified by the modulation as described in the text. The results represent the relative activities to 10^{-9} M of progesterone (the means ± SE of three replicates). PF1092A (**1**) stimulated LUC expression in the agonist format beyond 25% and suppressed in the antagonist format within 75%, therefore, was categorized as Type c. The ester (**8b**) and the carbamate (**19i**) demonstrated slightly stimulated LUC expression at only 10^{-6} M in the agonist format within 10% and inhibited in the antagonist format beyond

Table 6. Binding affinities for steroid receptors

Compound	IC_{50}[†] (nM)			
	Progesterone receptor (human)	Androgen receptor (rat)	Glucocorticoid receptor (mouse)	Estrogen receptor (human)
8b	32	6350	$>1\times10^4$	$>1\times10^4$
19i	81	8732	$>1\times10^4$	$>1\times10^4$
RU486	13	98	74	$>1\times10^4$

[†] IC_{50} values were measured from two independent experiments (Cerep).

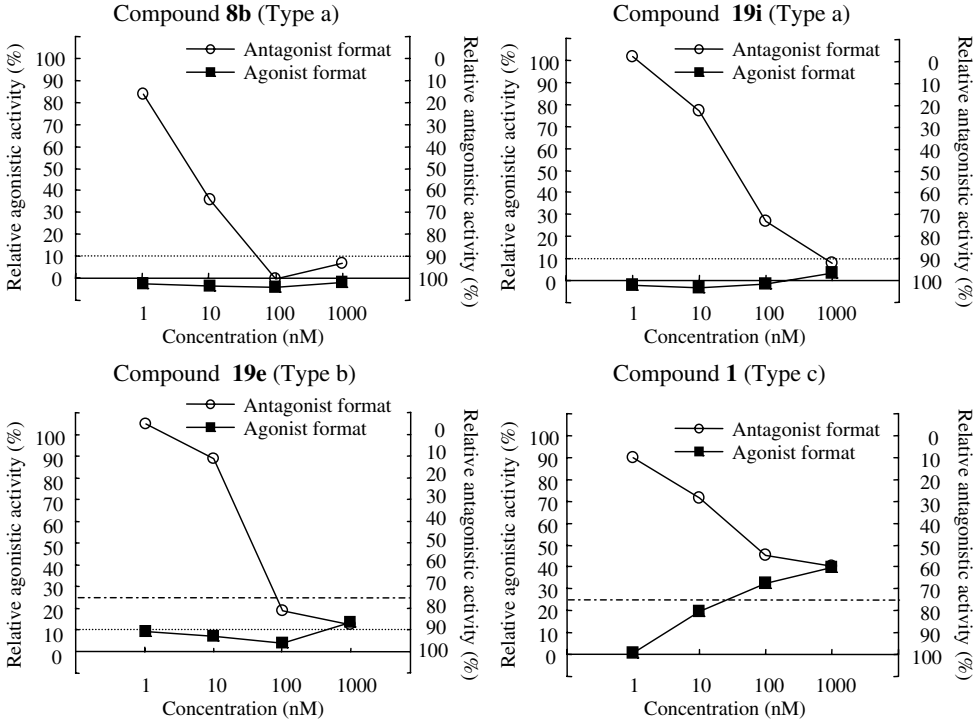


Figure 2. Representative dose-dependency for **1**, **8b**, **19e**, and **19i** in the LUC assay. The classification was defined as described in the text and the method was shown in Section 5.

90%, accordingly, classified as Type a. The other carbamate (**19e**) showed relative agonistic activity beyond 10% and antagonistic activity within 90% (Type b).

Steroid receptor selectivity assay was carried out for two compounds, **8b** and **19i**, selected from among the 6,7-*syn* and 6,7-*anti* derivatives, respectively. The results were measured by Cerep (France), a private service company that performs drug discovery (Table 6). Both compounds exhibited a high selectivity of at least 100-fold for PR over the androgen receptor. In addition, these compounds showed no binding interaction with the glucocorticoid and estrogen receptors at concentrations up to 10 μM. In contrast, a representative PR antagonist, RU486, had similar binding interactions with both the androgen receptor and the glucocorticoid receptor.

4. Conclusion

We modified the novel fungal metabolite PF1092C (**3**) as a part of our search for novel nonsteroidal PR antagonists. Furthermore, the SAR of tetrahydronaphthofuranones as human PR ligands was characterized. As a result of these studies, we identified two compounds, the 6,7-*syn* dipropionate **8b** and 6,7-*anti* derivative **19i**, which showed remarkable selectivity for PR over other related steroid hormone receptors. Both compounds were antagonists in an in vitro assay.[21,22] The carbamate **19i** was evaluated in vivo and was confirmed to show antagonistic activity.[22] Based on these promising results, further structural modification studies of tetrahydronaphthofuranones are planned in order to find compounds with more potent in vivo activity.

5. Experimental

5.1. Chemistry

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 polarimeter. ^{1}H NMR (300 MHz) spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shifts are reported in δ value (ppm) with tetramethylsilane (TMS) as the internal standard (NMR peak description: s, singlet; d, doublet; t, triplet; q, quartet; sep, septet; m, multiplet; br, broad peak). Elemental analyses were within ±0.4% of the theoretical values for the elements indicated, unless otherwise noted. High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-700. All commercial reagents and solvents were used as received. All reactions were done under inert, dry atmosphere unless an aqueous solution was used. PF1092C was prepared according to described procedure.[15]

5.1.1. (4a*R*,5*R*,6*R*,7*S*)-6-(Furan-2-ylcarbonyl)oxy-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (6b). To a solution of **3** (4.00 g, 15.3 mmol) in DMF (40 ml) were added *t*-butyldimethylsilyl chloride (TBDMSCl) (3.97 g, 26.3 mmol) and imidazole (3.55 g, 52.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6.5 h. The mixture was dissolved in AcOEt and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 7β-O-TBDMS-compound (**4**, 5.65 g, 98%) as a colorless solid.

To a solution of **4** (3.00 g, 7.96 mmol) in CH_2Cl_2 (60 ml) were added furan-2-carbonyl chloride (1.57 ml, 15.9 mmol) and 4-dimethylaminopyridine (DMAP) (2.93 g, 24.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The mixture was washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the furan-2-carboxylate (**5c**, 3.76 g, 100%) as a colorless solid.

The above intermediate was dissolved in THF (75 ml), and hydrogen fluoride–pyridine complex (Py–HF) (12.9 ml) was added at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with saturated aqueous $NaHCO_3$ and 5% aqueous $KHSO_4$, dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on silica gel and recrystallized from hot MeOH to give the title compound (**6b**) as a pale yellow crystalline solid (2.80 g, 98%): mp 183–185 °C (decomp.); $[\alpha]_D^{28}$ +211° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60 (1H, m), 7.20 (1H, br d, J = 3.6 Hz), 6.53 (1H, dd, J = 3.6, 1.6 Hz), 6.03 (1H, s), 5.73 (1H, br s), 5.52 (1H, ddd, J = 5.0, 1.7, 1.7 Hz), 4.63 (1H, m), 2.89 (1H, d, J = 16.1 Hz), 2.25 (1H, br d, J = 16.1 Hz), 2.10 (1H, dq, J = 7.1, 1.7 Hz), 1.94 (3H, d, J = 1.6 Hz), 1.28 (3H, s), 1.18 (3H, d, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{20}H_{20}O_6$: 357.1338. Found: 357.1341.

5.1.2. (4a*R*,5*R*,6*R*,7*S*)-7-Hydroxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (6a). Compound **6a** was prepared according to a similar procedure to **6b** to give a colorless amorphous solid: $[\alpha]_D^{29}$ +7.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.00 (1H, s), 5.68 (1H, br s), 5.31 (1H, ddd, J = 5.1, 1.6, 1.6 Hz), 4.56 (1H, m), 2.85 (1H, d, J = 16.4 Hz), 2.43, 2.43 (2H, each q, J = 7.6 Hz), 2.21 (1H, br d, J = 16.4 Hz), 2.01 (1H, dq, J = 7.1, 1.6 Hz), 1.93 (3H, d, J = 1.8 Hz), 1.18 (3H, d, J = 0.6 Hz), 1.18 (3H, t, J = 7.6 Hz), 1.12 (3H, d, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{18}H_{22}O_5$: 319.1545. Found: 319.1540.

5.1.3. (4a*R*,5*R*,6*R*,7*S*)-6-(Furan-2-ylcarbonyl)oxy-7-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (7d). To a solution of **6b** (60 mg, 0.19 mmol) in CH_2Cl_2 (1.0 ml) were added propionyl chloride (65 μl, 0.75 mmol) and DMAP (103 mg, 0.84 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the title compound (**7d**, 70 mg, 90%) as a pale

yellow amorphous solid: ^{1}H NMR ($CDCl_3$) δ 7.60 (1H, m), 7.17 (1H, br d, J = 3.5, 0.8 Hz), 6.53 (1H, dd, J = 3.5, 1.7 Hz), 6.03 (1H, s), 5.73 (1H, m), 5.62 (1H, br s), 5.59 (1H, ddd, J = 4.8, 1.8, 1.8 Hz), 2.91 (1H, d, J = 16.7 Hz), 2.28 (1H, br d, J = 16.7 Hz), 2.26 (2H, q, J = 7.5 Hz), 2.16 (1H, dq, J = 7.1, 1.8 Hz), 1.95 (3H, d, J = 1.5 Hz), 1.32 (3H, s), 1.17 (3H, d, J = 7.1 Hz), 1.07 (3H, t, J = 7.5 Hz); HRMS (FAB) Calcd for $C_{23}H_{24}O_7$: 413.1600. Found: 413.1594.

5.1.4. (4a*R*,5*R*,6*R*,7*S*)-6-Acetoxy-7-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (7a). Compound **7a** was prepared according to a similar procedure to **7d** to give a colorless solid: ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.63 (1H, m), 5.58 (1H, br s), 5.38 (1H, m), 2.87 (1H, d, J = 16.2 Hz), 2.32 (2H, m), 2.23 (1H, br d, J = 16.2 Hz), 2.11 (3H, s), 2.05 (1H, br q, J = 7.1 Hz), 1.93 (3H, d, J = 1.6 Hz), 1.20 (3H, s), 1.14 (3H, t, J = 7.5 Hz), 1.11 (3H, d, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{20}H_{24}O_6$: 361.1651. Found: 361.1651.

5.1.5. (4a*R*,5*R*,6*R*,7*S*)-7-Acetoxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (7b). Compound **7b** was prepared according to a similar procedure to **7d** to give a colorless solid: ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.63 (1H, m), 5.57 (1H, br s), 5.40 (1H, m), 2.87 (1H, d, J = 16.4 Hz), 2.39 (2H, q, J = 7.5 Hz), 2.23 (1H, br d, J = 16.4 Hz), 2.05 (1H, br q, J = 7.1 Hz), 2.03 (3H, s), 1.93 (3H, d, J = 1.9 Hz), 1.20 (3H, s), 1.18 (3H, t, J = 7.5 Hz), 1.11 (3H, d, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{20}H_{24}O_6$: 361.1651. Found: 361.1653.

5.1.6. (4a*R*,5*R*,6*R*,7*S*)-7-(Furan-2-ylcarbonyl)oxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (7c). Compound **7c** was prepared according to a similar procedure to **7d** to give a colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.58 (1H, dd, J = 1.7, 0.8 Hz,), 7.14 (1H, dd, J = 3.5, 0.8 Hz), 6.52 (1H, dd, J = 3.5, 1.7 Hz), 6.01 (1H, s), 5.83 (1H, m), 5.69 (1H, br s), 5.53 (1H, m), 2.90 (1H, d, J = 16.3 Hz), 2.43 (2H, q, J = 7.5 Hz), 2.27 (1H, br d, J = 16.3 Hz), 2.12 (1H, br q, J = 7.1 Hz), 1.94 (3H, d, J = 1.7 Hz), 1.23 (3H, s), 1.14 (3H, d, J = 7.1 Hz), 1.13 (3H, t, J = 7.5 Hz); HRMS (FAB) Calcd for $C_{23}H_{24}O_7$: 413.1600. Found: 413.1594.

5.1.7. (4a*R*,5*R*,6*R*,7*S*)-6,7-Dipropionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (8b). To a solution of **3** (2.00 g, 7.63 mmol) in CH_2Cl_2 (4.0 ml) were added propionic anhydride (9.8 ml, 76.4 mmol) and *N*,*N*-diisopropylethylamine (29.5 ml, 169 mmol) at 0 °C. The reaction mixture was stirred at 50 °C for 16 h. The mixture was diluted with CH_2Cl_2, washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was chromatographed on silica gel and recrystallized from hot 2-propanol to give the title compound (**8b**) as a colorless crystalline solid (2.55 g, 89%): mp 131–132 °C; $[\alpha]_D^{29}$ −4.9° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.64 (1H, m), 5.58 (1H, br s), 5.41 (1H, m), 2.87 (1H, d, J = 16.2 Hz), 2.39 (2H, q, J = 7.6 Hz), 2.31, 2.30 (2H, each q, J = 7.6 Hz), 2.24 (1H, br d, J = 16.2 Hz), 2.06 (1H, dq, J = 7.1, 1.8 Hz), 1.94 (3H, d, J = 1.7 Hz), 1.21 (3H, d, J = 0.9 Hz), 1.17 (3H, t, J = 7.6 Hz), 1.14 (3H, t, J = 7.6 Hz), 1.10 (3H, d, J = 7.1 Hz). Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00; O, 25.64. Found: C, 67.3; H, 7.00; O, 25.7.

5.1.8. (4a*R*,5*R*,6*R*,7*S*)-6,7-Diacetoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (8a). Compound **8a** was prepared according to a similar procedure to **8b** to give a colorless solid: $[\alpha]_D^{28}$ −16.4° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.62 (1H, m), 5.57 (1H, m), 5.38 (1H, ddd, J = 4.8, 1.8, 1.8 Hz), 2.87 (1H, d, J = 16.2 Hz), 2.23 (1H, br d, J = 16.2 Hz), 2.12 (3H, s), 2.04 (1H, dq, J = 7.2, 1.8 Hz), 2.04 (3H, s), 1.93 (3H, d, J = 1.7 Hz), 1.20 (3H, s), 1.11 (3H, d, J = 7.2 Hz); HRMS (FAB) Calcd for $C_{19}H_{22}O_6$: 347.1495. Found: 347.1498.

5.1.9. (4a*R*,5*R*,6*R*,7*S*)-6,7-Di(furan-2-ylcarbony)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (8c). Compound **8c** was prepared according to a similar procedure to **8b** to give a pale yellow amorphous solid: $[\alpha]_D^{27}$ +93.6° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60 (1H, m), 7.50 (1H, m), 7.18 (1H, br d, J = 3.4 Hz), 6.93 (1H, br d, J = 3.5 Hz), 6.53 (1H, dd, J = 3.4, 1.7 Hz), 6.42 (1H, dd, J = 3.5, 1.8 Hz), 6.04 (1H, s), 5.91 (1H, m), 5.73 (1H, m), 5.69 (1H, ddd, J = 4.8, 1.8, 1.8 Hz), 2.93 (1H, d, J = 16.2 Hz), 2.30 (1H, br d, J = 16.2 Hz), 2.21 (1H, dq, J = 7.1, 1.8 Hz), 1.95 (3H, d, J = 1.7 Hz), 1.35 (3H, s), 1.20 (3H, d, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{25}H_{22}O_8$: 451.1393. Found: 451.1386.

5.1.10. (4a*R*,5*R*,6*R*,7*S*)-6-Acetoxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (10). To a solution of **3** (161 mg, 0.61 mmol) in DMF (2.0 ml) were added methyl iodide (0.57 ml, 9.16 mmol) and 60% sodium hydride (NaH) (32 mg, 0.81 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h. The mixture was dissolved in AcOEt and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 7β-MeO-compound (**9**, R = Me, 148 mg, 87%) as a pale yellow solid.

To a solution of **9** (R = Me, 24 mg, 0.09 mmol) in CH_2Cl_2 (1.0 ml) were added acetyl chloride (27 μl, 0.38 mmol) and pyridine (35 μl, 0.43 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4.5 h. The mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided the title compound (**10**, 16 mg, 57%) as a pale yellow solid: $[\alpha]_D^{28}$ −18.8° (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.71 (1H, br s), 5.49 (1H, ddd, J = 4.6, 1.7, 1.7 Hz), 3.99 (1H, m), 3.42 (3H, s), 2.85 (1H, d, J = 16.4 Hz), 2.20 (1H, br d, J = 16.4 Hz), 2.12 (3H, s), 1.95 (1H, dq, J = 7.2, 1.7 Hz), 1.92 (3H, d, J = 1.7 Hz), 1.16 (3H, s), 1.11 (3H, d, J = 7.2 Hz); HRMS (FAB) Calcd for $C_{18}H_{22}O_5$: 319.1545. Found: 319.1549.

5.1.11. (4a*R*,5*R*,6*R*,7*R*)-6-Acetoxy-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (15a). To a solution of **3** (1.51 g, 5.75 mmol) in CH_2Cl_2 (30 ml) were added methanesulfonyl chloride (MsCl) (0.62 ml, 8.01 mmol)

and *N*,*N*-diisopropylethylamine (1.50 ml, 8.61 mmol) at 0 °C. The reaction mixture was maintained at 0 °C for 30 min. The mixture was diluted with CH_2Cl_2 and washed with 1 N NaOH. The organic layer was dried ($MgSO_4$), filtered, and concentrated. This residue, β-epoxide **11**, was used in the following step without further purification.

The above intermediate was dissolved in MeCN (30 ml), and 0.5 N HCl (6.9 ml, 3.5 mmol) was added at 0 °C. The reaction mixture was maintained at 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 7α-OH-compound (**12**, 1.02 g, 68%) as a colorless solid.

To a solution of **12** (501 mg, 1.91 mmol) in DMF (5.0 ml) were added TBDMSCl (595 mg, 3.95 mmol) and imidazole (529 mg, 7.77 mmol). The reaction mixture was stirred at room temperature for 1 day. The mixture was dissolved in AcOEt and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 7α-O-TBDMS-compound (**13**, 579 mg, 81%) as a colorless solid.

To a solution of **13** (32 mg, 0.08 mmol) in CH_2Cl_2 (1.0 ml) were added acetyl chloride (27 μl, 0.38 mmol) and pyridine (34 μl, 0.42 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 5.5 h. The mixture was diluted with CH_2Cl_2, and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided the acetate (**14a**, 30 mg, 85%).

The above intermediate was dissolved in THF (1.2 ml), and 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (79 μl, 0.08 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The mixture was dissolved in $CHCl_3$ and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided the title compound (**15a**, 24 mg, 85%) as a colorless solid: $[\alpha]_D^{27}$ −234° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.00 (1H, s), 5.84 (1H, br d, J = 4.5 Hz), 4.93 (1H, ddd, J = 2.8, 1.4, 1.4 Hz), 4.14 (1H, br d, J = 4.5 Hz), 2.87 (1H, d, J = 16.3 Hz), 2.25 (1H, br d, J = 16.3 Hz), 2.16 (1H, dq, J = 7.2, 2.8 Hz), 2.08 (3H, s), 1.93 (3H, d, J = 1.9 Hz), 1.12 (3H, s), 1.11 (3H, d, J = 7.2 Hz); HRMS (FAB) Calcd for $C_{17}H_{20}O_5$: 305.1389. Found: 305.1399.

5.1.12. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclopropylaminocarbonyloxy-7-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (15c). To a solution of **13** (247 mg, 0.66 mmol) in CH_2Cl_2 (5.0 ml) was added 1,1′-carbonyldiimidazole (CDI) (231 mg, 1.43 mmol). The reaction mixture was stirred at room temperature for 4.5 h. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 1*H*-imidazole-1-carboxylate (298 mg, 96%) as a colorless solid.

The above intermediate (109 mg, 0.25 mmol) was dissolved in toluene (2.0 ml), and cyclopropylamine (170 μl, 2.45 mmol) was added. The reaction mixture was stirred at room temperature for 10.5 h. The mixture was dissolved in CH_2Cl_2 and washed with 5% aqueous $KHSO_4$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the carbamate (**14c**, 54 mg, 51%).

The title compound (**15c**, 40 mg, 99%) was prepared according to a similar deprotection to **15a** to give a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.84 (1H, br d, J = 4.4 Hz), 5.00 (1H, m), 4.82 (1H, m), 4.23 (1H, m), 2.85 (1H, d, J = 16.2 Hz), 2.55 (1H, m), 2.26 (1H, br d, J = 16.2 Hz), 2.15 (1H, m), 1.93 (3H, br s), 1.15 (3H, br s), 1.06 (3H, br s), 0.70 (2H, m), 0.54 (2H, m); HRMS (FAB) Calcd for $C_{19}H_{23}NO_5$: 346.1654. Found: 346.1648.

5.1.13. (4a*R*,5*R*,6*R*,7*R*)-7-Hydroxy-6-propylaminocarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (15b). Compound **15b** was prepared according to a similar procedure to **15c** to give a pale yellow amorphous solid: ^{1}H NMR ($CDCl_3$) δ 5.97 (1H, s), 5.84 (1H, br d, J = 4.7 Hz), 4.82 (1H, m), 4.19 (1H, m), 3.59 (1H, m), 3.12 (2H, br dt, J = 7.4 Hz), 2.84 (1H, d, J = 16.4 Hz), 2.24 (1H, br d, J = 16.4 Hz), 2.15 (1H, dq, J = 6.9, 2.9 Hz), 1.91 (3H, br s), 1.50 (2H, sep, J = 7.4 Hz), 1.11 (3H, d, J = 6.9 Hz), 1.06 (3H, s), 0.90 (3H, t, J = 7.4 Hz); HRMS (FAB) Calcd for $C_{19}H_{25}NO_5$: 348.1811. Found: 348.1817.

5.1.14. (4a*R*,5*R*,6*R*,7*R*)-7-Acetoxy-6-hydroxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (16). The β-epoxide **11** was prepared from **3** (57 mg, 0.22 mmol) by the same procedure as **15a**. The above intermediate was dissolved in MeCN (0.55 ml), and potassium acetate (AcOK) (89 mg, 0.90 mmol) and 18-crown-6 (6.4 mg, 0.02 mmol) were added. The reaction mixture was stirred at room temperature for 5 h. The mixture was dissolved in $CHCl_3$ and washed with 5% aqueous $KHSO_4$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided the title compound (**16**, 27 mg, 41%) as a pale brown solid: ^{1}H NMR ($CDCl_3$) δ 6.02 (1H, s), 5.78 (1H, br d, J = 4.9 Hz), 5.21 (1H, dd, J = 4.9, 1.6 Hz), 3.86 (1H, m), 2.88 (1H, d, J = 16.8 Hz), 2.26 (1H, br d, J = 16.8 Hz), 2.08 (3H, s), 1.94 (3H, d, J = 1.9 Hz), 1.91 (1H, dq, J = 7.1, 2.8 Hz), 1.23 (3H, d, J = 7.1 Hz), 1.18 (3H, s); HRMS (FAB) Calcd for $C_{17}H_{20}O_5$: 305.1389. Found: 305.1380.

5.1.15. (4a*R*,5*R*,6*R*,7*R*)-6,7-Diacetoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (17). To a solution of **16** (26 mg, 0.09 mmol) in CH_2Cl_2 (1.0 ml) were added acetyl chloride (27 μl, 0.38 mmol) and pyridine (35 μl, 0.43 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3.5 h. The

mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided the title compound (**17**, 26 mg, 87%) as a colorless solid: $[\alpha]_D^{28}$ −482° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.83 (1H, d, J = 4.8 Hz), 5.14 (1H, dd, J = 4.8, 1.6 Hz), 5.07 (1H, m), 2.88 (1H, d, J = 16.5 Hz), 2.27 (1H, br d, J = 16.5 Hz), 2.11 (1H, dq, J = 7.1, 2.7 Hz), 2.08 (3H, s), 2.06 (3H, s), 1.93 (3H, d, J = 1.9 Hz), 1.13 (3H, s), 1.11 (3H, d, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{19}H_{22}O_6$: 347.1495. Found: 347.1498.

5.1.16. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19b). The β-epoxide **11** was prepared from **3** (2.00 g, 7.63 mmol) by the same procedure as **15a**. The above intermediate was dissolved in CH_2Cl_2 (30 ml), and MeOH (3.1 ml, 76.5 mmol) and 0.5 M solution of hydrogen chloride in MeOH (7.63 ml, 3.82 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 7α-MeO-compound (**18**, R = Me, 1.90 g, 90%) as a pale brown solid.

To a solution of the 7α-MeO-compound (42 mg, 0.15 mmol) in CH_2Cl_2 (0.85 ml) were added propionyl chloride (59 μl, 0.68 mmol) and pyridine (61 μl, 0.75 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided the title compound (**19b**, 23 mg, 45%) as a pale yellow solid: $[\alpha]_D^{29}$ −232° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.00 (1H, s), 5.84 (1H, br d, J = 4.7 Hz), 5.11 (1H, ddd, J = 2.8, 1.4, 1.4 Hz), 3.61 (1H, dd, J = 4.7, 1.4 Hz), 3.52 (3H, s), 2.86 (1H, d, J = 16.4 Hz), 2.36 (2H, q, J = 7.5 Hz), 2.25 (1H, br d, J = 16.4 Hz), 2.10 (1H, dq, J = 7.1, 2.8 Hz), 1.93 (3H, d, J = 1.7 Hz), 1.16 (3H, t, J = 7.5 Hz), 1.14 (3H, s), 1.12 (3H, d, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{19}H_{24}O_5$: 333.1702. Found: 333.1707.

5.1.17. (4a*R*,5*R*,6*R*,7*R*)-6-Acetoxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19a). Compound **19a** was prepared according to a similar procedure to **19b** to give a pale brown solid: $[\alpha]_D^{28}$ −258° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.00 (1H, s), 5.84 (1H, br d, J = 4.8 Hz), 5.09 (1H, ddd, J = 2.8, 1.4, 1.4 Hz), 3.61 (1H, dd, J = 4.8, 1.4 Hz), 3.50 (3H, s), 2.86 (1H, d, J = 16.4 Hz), 2.24 (1H, br d, J = 16.4 Hz), 2.09 (1H, dq, J = 7.1, 2.8 Hz), 2.08 (3H, s), 1.92 (3H, d, J = 1.7 Hz), 1.12 (3H, s), 1.11 (3H, d, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{18}H_{22}O_5$: 319.1545. Found: 319.1549.

5.1.18. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclopropylcarbonyloxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19c). Compound **19c** was prepared according to a similar procedure to **19b** to give a pale yellow amorphous solid: $[\alpha]_D^{29}$ −134° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.00 (1H, s), 5.84 (1H, br d, J = 4.8 Hz), 5.09 (1H, ddd, J = 2.8, 1.4, 1.4 Hz), 3.61 (1H, dd, J = 4.8, 1.4 Hz), 3.50 (3H, s), 2.86 (1H, d, J = 16.4 Hz), 2.24 (1H, br d, J = 16.4 Hz), 2.09 (1H, dq, J = 7.2, 2.8 Hz), 1.93 (3H, d, J = 1.9 Hz), 1.59 (1H, m), 1.15 (3H, s), 1.12 (3H, d, J = 7.2 Hz), 1.00 (2H, m), 0.90 (2H, m); HRMS (FAB) Calcd for $C_{20}H_{24}O_5$: 345.1702. Found: 345.1706.

5.1.19. (4a*R*,5*R*,6*R*,7*R*)-6-(Furan-2-ylcarbonyl)oxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19d). Compound **19d** was prepared according to a similar procedure to **19b** to give a pale yellow amorphous solid: $[\alpha]_D^{27}$ +18.6° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.60 (1H, dd, J = 1.8, 0.8 Hz), 7.14 (1H, dd, J = 3.5, 0.8 Hz), 6.52 (1H, dd, J = 3.5, 1.8 Hz), 6.03 (1H, s), 5.87 (1H, br d, J = 4.8 Hz), 5.32 (1H, ddd, J = 2.7, 1.4, 1.4 Hz), 3.75 (1H, dd, J = 4.8, 1.4 Hz), 3.57 (3H, s), 2.90 (1H, d, J = 16.3 Hz), 2.28 (1H, br d, J = 16.3 Hz), 2.20 (1H, dq, J = 7.2, 2.7 Hz), 1.95 (3H, d, J = 2.0 Hz), 1.25 (3H, s), 1.18 (3H, d, J = 7.2 Hz); HRMS (FAB) Calcd for $C_{21}H_{22}O_6$: 371.1495. Found: 371.1489.

5.1.20. (4a*R*,5*R*,6*R*,7*R*)-6-Ethoxycarbonyloxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19e). Compound **19e** was prepared according to a similar procedure to **19b** to give a pale yellow amorphous solid: ^1H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.84 (1H, br d, J = 4.8 Hz), 4.90 (1H, ddd, J = 2.8, 1.4, 1.4 Hz), 4.21 (2H, q, J = 7.1 Hz), 3.72 (1H, dd, J = 4.8, 1.4 Hz), 3.52 (3H, s), 2.86 (1H, d, J = 16.4 Hz), 2.23 (1H, br d, J = 16.4 Hz), 2.10 (1H, dq, J = 7.2, 2.8 Hz), 1.93 (3H, d, J = 1.9 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.17 (3H, d, J = 7.2 Hz), 1.13 (3H, s); HRMS (FAB) Calcd for $C_{19}H_{24}O_6$: 349.1651. Found: 349.1641.

5.1.21. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-phenoxycarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19f). Compound **19f** was prepared according to a similar procedure to **19b** to give a colorless amorphous solid: ^1H NMR ($CDCl_3$) δ 7.43–7.36 (2H, m), 7.28–7.16 (3H, m), 6.02 (1H, s), 5.87 (1H, br d, J = 4.6 Hz), 4.98 (1H, ddd, J = 2.7, 1.4, 1.4 Hz), 3.82 (1H, dd, J = 4.6, 1.4 Hz), 3.53 (3H, s), 2.88 (1H, d, J = 16.3 Hz), 2.26 (1H, br d, J = 16.3 Hz), 2.16 (1H, dq, J = 7.2, 2.7 Hz), 1.94 (3H, d, J = 1.9 Hz), 1.24 (3H, d, J = 7.2 Hz), 1.10 (3H, s); HRMS (FAB) Calcd for $C_{23}H_{24}O_6$: 397.1651. Found: 397.1646.

5.1.22. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-methylaminocarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19g). To a solution of 7α-MeO-compound (**18**, R = Me, 1.00 g, 3.62 mmol) in CH_2Cl_2 (20 ml) was added CDI (1.24 g, 7.64 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 7α-MeO-1*H*-imidazole-1-carboxylate (1.25 g, 93%) as a pale brown solid.

The above intermediate (52 mg, 0.14 mmol) was dissolved in CH_2Cl_2 (2.0 ml), and methyl trifluoromethane-

sulfonate (TfOMe) (24 μl, 0.21 mmol) was added at 0 °C. The reaction mixture was maintained at 0 °C for 30 min and 2 M solution of methylamine in THF (0.35 ml, 0.70 mmol) was added. The mixture was stirred at room temperature for 30 min, diluted with CH_2Cl_2, and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided the title compound (**19g**, 43 mg, 91%) as a pale yellow amorphous solid: ^{1}H NMR ($CDCl_3$) δ 5.97 (1H, s), 5.83 (1H, br d, J = 4.9 Hz), 4.97 (1H, m), 4.73 (1H, m), 3.68 (1H, br d, J = 4.9 Hz), 3.51 (3H, s), 2.84 (1H, d, J = 16.2 Hz), 2.81 (3H, d, J = 4.9 Hz), 2.21 (1H, br d, J = 16.2 Hz), 2.05 (1H, dq, J = 7.2, 2.7 Hz), 1.91 (3H, d, J = 1.6 Hz), 1.13 (3H, d, J = 7.2 Hz), 1.07 (3H, s); HRMS (FAB) Calcd for $C_{18}H_{23}NO_5$: 334.1654. Found: 334.1656.

5.1.23. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-propylaminocarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19h). Compound **19h** was prepared according to a similar procedure to **19g** to give a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ 5.98 (1H, s), 5.84 (1H, br d, J = 4.7 Hz), 4.98 (1H, m), 4.70 (1H, m), 3.68 (1H, br d, J = 4.7 Hz), 3.52 (3H, s), 3.16 (2H, br dt, J = 7.3 Hz), 2.85 (1H, d, J = 16.3 Hz), 2.22 (1H, br d, J = 16.3 Hz), 2.06 (1H, dq, J = 7.1, 2.7 Hz), 1.92 (3H, d, J = 1.6 Hz), 1.52 (2H, sep, J = 7.3 Hz), 1.14 (3H, d, J = 7.1 Hz), 1.09 (3H, s), 0.92 (3H, t, J = 7.3 Hz); HRMS (FAB) Calcd for $C_{20}H_{27}NO_5$: 362.1967. Found: 362.1973.

5.1.24. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclopropylaminocarbonyloxy-7-methoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19i). Compound **19i** was prepared according to a similar procedure to **19g** to give a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.84 (1H, br d, J = 4.4 Hz), 4.98 (1H, m), 4.87 (1H, m), 3.70 (1H, br d, J = 4.4 Hz), 3.54 (3H, s), 2.85 (1H, d, J = 16.3 Hz), 2.60 (1H, m), 2.24 (1H, br d, J = 16.3 Hz), 2.08 (1H, m), 1.93 (3H, d, J = 1.2 Hz), 1.15 (3H, br d, J = 5.8 Hz), 1.08 (3H, br s), 0.74 (2H, m), 0.55 (2H, m); HRMS (FAB) Calcd for $C_{20}H_{25}NO_5$: 360.1811. Found: 360.1816.

5.1.25. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(*N*-methyl-*N*-propylaminocarbonyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19j). Compound **19j** was prepared according to a similar procedure to **19g** to give a pale yellow amorphous solid: ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.83 (1H, br d, J = 4.8 Hz), 4.98 (1H, m), 3.68 (1H, m), 3.54 (3H, s), 3.30–3.08 (2H, m), 2.92, 2.82 (3H, each s), 2.86 (1H, d, J = 16.3 Hz), 2.24 (1H, br d, J = 16.3 Hz), 2.13 (1H, dq, J = 7.1, 2.8 Hz), 1.92 (3H, d, J = 1.7 Hz), 1.53 (2H, m), 1.14 (3H, d, J = 7.1 Hz), 1.12 (3H, s), 0.89, 0.80 (3H, each t, J = 7.4 Hz); HRMS (FAB) Calcd for $C_{21}H_{29}NO_5$: 376.2124. Found: 376.2118.

5.1.26. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-(pyrrolidine-1-ylcarbonyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19k). Compound **19k** was prepared according to a similar procedure to **19g** to give a colorless solid: ^{1}H NMR ($CDCl_3$) δ 6.00 (1H, s), 5.84 (1H, br d, J = 4.8 Hz), 3.74 (1H, dd, J = 4.8, 1.4 Hz), 3.56 (3H, s), 3.42 (2H, br t, J = 5.7 Hz), 3.28 (2H, br t, J = 6.8 Hz), 2.86 (1H, d, J = 16.2 Hz), 2.25 (1H, br d, J = 16.2 Hz), 2.10 (1H, dq, J = 7.1, 2.8 Hz), 1.98 (1H, ddd, J = 2.7, 1.4, 1.4 Hz), 1.93 (3H, d, J = 1.7 Hz), 1.92–1.85 (4H, m), 1.16 (3H, d, J = 7.1 Hz), 1.14 (3H, s); HRMS (FAB) Calcd for $C_{21}H_{27}NO_5$: 374.1967. Found: 374.1965.

5.1.27. (4a*R*,5*R*,6*R*,7*R*)-7-Methoxy-6-phenylaminocarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19l). Compound **19l** was prepared according to a similar procedure to **19g** to give a colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.44 (2H, m), 7.31 (2H, m), 7.08 (1H, m), 6.89 (1H, m), 6.00 (1H, s), 5.88 (1H, br d, J = 4.9 Hz), 5.11 (1H, ddd, J = 2.7, 1.4, 1.4 Hz), 3.76 (1H, dd, J = 4.9, 1.4 Hz), 3.55 (3H, s), 2.86 (1H, d, J = 16.3 Hz), 2.25 (1H, br d, J = 16.3 Hz), 2.13 (1H, dq, J = 7.1, 2.7 Hz), 1.93 (3H, d, J = 1.4 Hz), 1.19 (3H, d, J = 7.1 Hz), 1.10 (3H, s); HRMS (FAB) Calcd for $C_{23}H_{25}NO_5$: 396.1811. Found: 396.1811.

5.1.28. (4a*R*,5*R*,6*R*,7*R*)-7-Ethoxy-6-propylaminocarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19m). Compound **19m** was prepared according to a similar procedure to **19g** to give a pale yellow amorphous solid: ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.83 (1H, br d, J = 4.8 Hz), 4.96 (1H, m), 4.70 (1H, m), 3.88 (1H, m), 3.78 (1H, br d, J = 4.8 Hz), 3.65 (1H, m), 3.16 (2H, br dt, J = 7.1 Hz), 2.84 (1H, d, J = 16.3 Hz), 2.25 (1H, br d, J = 16.3 Hz), 2.10 (1H, dq, J = 7.0, 2.6 Hz), 1.92 (3H, d, J = 1.7 Hz), 1.53 (2H, sep, J = 7.1 Hz), 1.22 (3H, br t, J = 7.0 Hz), 1.14 (3H, d, J = 7.0 Hz), 1.09 (3H, s), 0.93 (3H, t, J = 7.1 Hz); HRMS (FAB) Calcd for $C_{21}H_{29}NO_5$: 376.2124. Found: 376.2125.

5.1.29. (4a*R*,5*R*,6*R*,7*R*)-7-(1-Methylethoxy)-6-propylaminocarbonyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19n). Compound **19n** was prepared according to a similar procedure to **19g** to give a pale yellow amorphous solid: ^{1}H NMR ($CDCl_3$) δ 5.96 (1H, s), 5.75 (1H, br d, J = 4.9 Hz), 4.85 (1H, m), 4.73 (1H, m), 4.01 (1H, m), 3.84 (1H, br d, J = 4.9 Hz), 3.15 (2H, br dt, J = 7.3 Hz), 2.83 (1H, d, J = 16.2 Hz), 2.24 (1H, br d, J = 16.2 Hz), 2.11 (1H, dq, J = 7.2, 2.4 Hz), 1.91 (3H, br s), 1.53 (2H, sep, J = 7.3 Hz), 1.19, 1.17 (6H, each d, J = 6.6 Hz), 1.13 (3H, d, J = 7.2 Hz), 1.07 (3H, s), 0.91 (3H, t, J = 7.3 Hz); HRMS (FAB) Calcd for $C_{22}H_{31}NO_5$: 390.2280. Found: 390.2287.

5.1.30. (4a*R*,5*R*,6*R*,7*R*)-6-Cyclopropylaminocarbonyloxy-7-ethoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (19o). Compound **19o** was prepared according to a similar procedure to **19g** to give a colorless amorphous solid: ^{1}H NMR ($CDCl_3$) δ 5.99 (1H, s), 5.83 (1H, br d, J = 4.1 Hz), 4.96 (1H, m), 4.84 (1H, m), 3.89 (1H, m), 3.80 (1H, br d, J = 4.1 Hz), 3.67 (1H, m), 2.85 (1H, d, J = 16.6 Hz), 2.60 (1H, m), 2.26 (1H, br d, J = 16.6 Hz), 2.12 (1H, m), 1.93 (3H, br s), 1.22 (3H, br t, J = 7.0 Hz), 1.15 (3H, br s), 1.08 (3H, br s), 0.73 (2H, m), 0.55 (2H, m); HRMS (FAB) Calcd for $C_{21}H_{27}NO_5$: 374.1967. Found: 374.1965.

5.1.31. (4a*R*,5*R*,6*S*)-6-Acetoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (22a). To a solution of **3** (1.16 g, 4.41 mmol) in toluene (160 ml) was added *p*-tol-

uenesulfonic acid (*p*-TsOH) monohydrate (174 mg, 0.91 mmol). The reaction mixture was stirred at 60 °C for 10 min. The mixture was cooled and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 7-deoxy-6-oxo-compound (**20**, 0.83 g, 77%) as a pale yellow solid.

The above intermediate was dissolved in MeOH (16 ml), and sodium borohydride ($NaBH_4$) (268 mg, 7.08 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with 5% aqueous $KHSO_4$ and extracted with CH_2Cl_2. The organic layer was washed with saturated 5% aqueous $KHSO_4$ and brine, dried ($MgSO_4$), filtered, and concentrated. Flash chromatography on silica gel of this residue provided the 7-deoxy-6β-OH-compound (**21**, 457 mg, 55%) and its epimer 7-deoxy-6α-OH-compound (**23**, 12 mg, 1.4%).

To a solution of **21** (31 mg, 0.13 mmol) in CH_2Cl_2 (0.6 ml) were added acetyl chloride (40 μl, 0.56 mmol) and pyridine (51 μl, 0.63 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $KHSO_4$ and saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Preparative TLC of this residue provided the title compound (**22a**, 16 mg, 45%) as a pale yellow solid: $[\alpha]_D^{27}$ −44.1° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.96 (1H, s), 5.70 (1H, m), 5.12 (1H, m), 2.84 (1H, d, *J* = 16.3 Hz), 2.58 (1H, br ddd, *J* = 20.0, 3.6 Hz), 2.38 (1H, dd, *J* = 20.0, 4.7 Hz), 2.19 (1H, br d, *J* = 16.3 Hz), 2.04 (3H, s), 1.90 (3H, d, *J* = 1.4 Hz), 1.89 (1H, dq, *J* = 7.2, 2.5 Hz), 1.14 (3H, s), 1.08 (3H, d, *J* = 7.2 Hz); HRMS (FAB) Calcd for $C_{17}H_{20}O_4$: 289.1440. Found: 289.1444.

5.1.32. (4a*R*,5*R*,6*S*)-6-Propionyloxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (22b). Compound **22b** was prepared according to a similar procedure to **22a** to give a pale yellow solid: $[\alpha]_D^{28}$ −28.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.97 (1H, s), 5.70 (1H, m), 5.14 (1H, m), 2.84 (1H, d, *J* = 16.3 Hz), 2.59 (1H, br ddd, *J* = 20.0, 3.6 Hz), 2.38 (1H, dd, *J* = 20.0, 4.7 Hz), 2.33 (2H, q, *J* = 7.5 Hz), 2.21 (1H, br d, *J* = 16.3 Hz), 1.91 (3H, d, *J* = 1.4 Hz), 1.90 (1H, dq, *J* = 7.2, 2.5 Hz), 1.14 (3H, s), 1.13 (3H, t, *J* = 7.5 Hz), 1.08 (3H, d, *J* = 7.2 Hz); HRMS (FAB) Calcd for $C_{18}H_{22}O_4$: 303.1596. Found: 303.1590.

5.1.33. (4a*R*,5*R*,6*S*)-6-(Furan-2-ylcarbonyl)oxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (22c). Compound **22c** was prepared according to a similar procedure to **22a** to give a pale brown solid: $[\alpha]_D^{27}$ +270° (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.57 (1H, dd, *J* = 1.7, 0.8 Hz), 7.11 (1H, dd, *J* = 3.3, 0.8 Hz), 6.50 (1H, dd, *J* = 3.3, 1.7 Hz), 5.96 (1H, s), 5.74 (1H, m), 5.38 (1H, m), 2.88 (1H, d, *J* = 16.4 Hz), 2.69 (1H, br ddd, *J* = 20.8 Hz), 2.54 (1H, dd, *J* = 20.8, 5.0 Hz), 2.26 (1H, br d, *J* = 16.4 Hz), 2.00 (1H, dq, *J* = 7.2, 2.5 Hz), 1.93 (3H, d, *J* = 1.7 Hz), 1.27 (3H, s), 1.16 (3H, d, *J* = 7.2 Hz); HRMS (FAB) Calcd for $C_{20}H_{20}O_5$: 341.1389. Found: 341.1384.

5.1.34. (4a*R*,5*R*,6*R*)-6-Acetoxy-4a,5,6,7-tetrahydro-3,4a,5-trimethylnaphtho[2,3-*b*]furan-2(4*H*)-one (24). Compound **24** was prepared according to a similar procedure to **22a** using 7-deoxy-6α-OH-compound **23** to give a colorless oil: ^1H NMR ($CDCl_3$) δ 5.95 (1H, s), 5.69 (1H, m, *J* = 5.6, 3.3 Hz), 5.00 (1H, ddd, *J* = 11.9, 9.6, 6.0 Hz), 2.87 (1H, d, *J* = 16.4 Hz), 2.77 (1H, ddd, *J* = 19.0, 6.0, 5.6 Hz), 2.29 (1H, br d, *J* = 16.4 Hz), 2.16 (1H, ddd, *J* = 19.0, 9.6, 3.3 Hz), 2.10 (3H, s), 1.93 (1H, dq, *J* = 11.9, 6.8 Hz), 1.93 (3H, d, *J* = 1.9 Hz), 1.04 (3H, s), 1.03 (3H, d, *J* = 6.8 Hz); HRMS (FAB) Calcd for $C_{17}H_{20}O_4$: 289.1440. Found: 289.1438.

5.2. Biological method

5.2.1. Materials. Progesterone was purchased from Junsei Chemical. RU486 (11β-[4-dimethylamino]phenyl-17β-hydroxy-17-[1-propynyl]estra-4,9-diene-3-one) was purchased from Sigma. [1,2,6,7-^{3}H(N)]Progesterone (specific activity: 3848 GBq/mmol) was purchased from Perkin-Elmer.

5.2.2. Cell cultures. T47D human breast carcinoma cells were purchased from the American Type Culture Collection (ATCC). The T47D line was cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum. This cell line was cultured at 37 °C with 5% CO_2.

5.2.3. PR binding assay. The measurements of the binding affinity of compounds for the PR were performed as described earlier.[21] Unless otherwise specified, the following procedures were conducted at temperatures of 0–4 °C. Collected T47D cells were sonicated with a Branson Sonifier 450 in a buffer consisting of 5 mM KH_2PO_4 (pH 7.4), 30% glycerol, 0.1% α-thioglycerol, and 25 μg/ml leupeptin, followed by centrifugation at 100,000*g* for 30 min. The resulting supernatant (cytosol) was stored at −80 °C prior to its use as a source of progesterone receptors for the binding assays.

A reaction mixture (100 μl) containing 50 mM KH_2PO_4 (pH 7.4), 10% glycerol, 0.1% α-thioglycerol, 25 μg/ml leupeptin, 1 mM EDTA, [1,2,6,7-^{3}H(N)]progesterone (final concentration of 1.4 nM), T47D cytosol (0.8 mg protein/ml), and a test sample was incubated for 1 h at 4 °C. After incubation, 100 μl of dextran-coated charcoal solution consisting of 0.5% Norit A (Nacalai Tesque) and 0.05% Dextran T-70 (Pharmacia Fine Chemicals) was added to the incubation mixture, and incubation was continued for 10 min at 4 °C. The mixture was then centrifuged at 1800 rpm for 5 min. The radioactivity of 100 μl of the supernatant was measured in 2 ml of Aquasol-2 (Perkin-Elmer) with a liquid scintillation counter (Beckman LS6500). Nonspecific binding was defined as the binding observed when 10 μM of cold progesterone was added to the reaction mixture. Sigmoid fitting curves of the results expressed as inhibitory effects of the test compounds were obtained using KaleidaGraph software (Synergy Software). IC_{50} values were determined from the sigmoid fitting curve parameters. Relative binding affinity (RBA) was calculated by the comparison of IC_{50} values of the test compounds and progesterone.

5.2.4. Progesterone-dependent exogenous luciferase expression assay. The progesterone-dependent modulation of gene transcription was examined using the luciferase assay with stably transfected T47D-pMAMneo-LUC cells. The assay was performed as previously described.[21] In brief, the growth medium for T47D-pMAMneo-LUC cells was replaced with phenol red-free DMEM containing 5% fetal bovine serum treated with dextran-coated charcoal. After 24 h of cultivation, the cells were plated in 96-well plates at 50,000 cells/well. After 8 h of cultivation, the test compounds were added to each well to achieve the appropriate compound concentration. After 16 h of cultivation, 100 μl of Luc Lite (Perkin-Elmer) solution was added to each well and mixed. After 15 min of incubation at room temperature, luminescence was measured using luminometer.

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